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Original article

Long-term outcomes of patients with Takayasu arteritis and renal artery involvement: a cohort study

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Abstract

Objective. To describe the long-term outcomes of patients with Takayasu arteritis (TAK) and renal artery involvement (RAI).

Methods. A retrospective review of 122 patients with TAK at three tertiary centres in Canada, Sweden and the UK. Data on demographics, laboratory and clinical parameters, medications and angiography findings were collected. Non-renal and renal parameters were compared at baseline and follow-up.

Results. A total of 37 patients (30%) with RAI were identified: 18 (49%) with unilateral and 19 (51%) with bilateral RAI. Patients were predominantly female (89%). The median age at diagnosis was 27 years [interquartile range (IQR) 16–38]. The median follow-up time was 7 years (IQR 2–12). Hypertension was seen in 27 patients (73%) at presentation and 25 (68%) at follow-up. The median estimated glomerular filtration (eGFR) at presentation was 94 and 98 ml/min/1.73 m^2 in those with unilateral and bilateral RAI, respectively. The corresponding median eGFR at follow-up was 101.5 and 104 ml/min/1.73 m^2, respectively. Three patients at presentation and two at follow-up had an eGFR of $<$60 ml/min/1.73 m^2. Five underwent endovascular intervention and three required surgical interventions. Among the 33 patients with radiologic follow-up, 23 (69%) had persistent RAI and 10 (30%) had resolution of RAI. One (6%) patient with unilateral RAI developed bilateral RAI and three (19%) with bilateral RAI regressed to unilateral RAI. Over time, 23 (62%) patients had stable renal function, 7 (19%) had improvement and 4 had a decline in renal function; no patient developed end-stage renal disease (ESRD).

Conclusion. In this series of TAK patients with RAI, long-term non-renal and renal outcomes were favourable. No patient experienced ESRD or died.

Key words: renal, Takayasu arteritis, vasculitis

ORIGINAL ARTICLE

Introduction

Takayasu arteritis (TAK) is a chronic inflammatory large vessel vasculitis of unknown aetiology characterized by granulomatous inflammation of the aorta and its branches [1]. It predominantly affects women $<$40 years of age. It has an incidence of 0.3–2.6 cases per million in Europe and North America; the incidence is higher in Asian and Indian populations [2–4].

TAK is characterized by an early inflammatory phase manifested as non-specific systemic symptoms that often lead to a delay in diagnosis. The chronic inflammatory process leads to vascular stenosis over a period of months (aneurysms can also occur), resulting in end-organ damage and symptoms of ischaemia characterized by limb claudication, abdominal or chest pain, stroke and/or presyncope [4]. During this later phase, patients are often found to have reduced or absent arterial pulses, asymmetric blood pressures or aortic murmurs secondary to aortic root involvement. Long-term morbidity results from systemic and pulmonary

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Key messages

- The prevalence of renal artery involvement in this Takayasu arteritis cohort is comparable to that of published cohorts.
- Long-term outcomes of renal artery involvement in this Takayasu arteritis cohort were relatively good.
- No patient developed end-stage renal disease during the study period.

hypertension, angina, aortic insufficiency, stroke and reduced quality of life [4, 5].

The reported incidence of renal artery involvement (RAI) in TAK is 8–38% [3, 4, 6–11]. RAI is described as a poor prognostic factor that leads to renal artery stenosis, renovascular hypertension often refractory to antihypertensive therapy [4, 6, 7, 12] and renal insufficiency [11]. There are correlations between renovascular hypertension and cardiovascular morbidity and mortality; pregnancy is often discouraged due to feared complications such as pre-eclampsia [13]. However, there are limited data on the long-term outcomes of patients with TAK and RAI [11]. Here we report the long-term outcomes of 37 patients with TAK and RAI from three centres in Canada, Sweden and the UK.

Methods

A retrospective review of all patients with TAK was performed at the Vasculitis Clinic, Addenbrooke's Hospital, Cambridge, UK; the Department of Rheumatology, Lund University Hospital, Lund, Sweden and the Vasculitis Clinic, Mount Sinai Hospital, Toronto, Ontario, Canada. The diagnosis of TAK was based on constitutional symptoms, elevated inflammatory markers and positive angiography showing arterial wall thickening and stenosis, with/without aneurysm. A diagnosis of RAI required positive angiography—either conventional catheter angiography, CT angiography or magnetic resonance angiography. All imaging was systematically evaluated for RAI.

Data collection

Medical records were reviewed at baseline and follow-up. The baseline was defined as the time of diagnosis of RAI. Follow-up was defined as the last patient visit. Data were collected on demographics, comorbidities, presenting symptoms and signs, presence of hypertension and prior and current medications. Laboratory values including creatinine, ESR, and CRP were reviewed. Data on vessel wall involvement and severity were obtained from imaging reports. Data were used to determine whether the ACR classification criteria for TAK were met [14]. When available, results from histology, technetium-99m (Tc99m) mercaptoacetyltriglycine scans and endovascular interventions were reviewed. Estimated glomerular filtration (eGFR) was calculated based on the Chronic Kidney Disease Epidemiology Collaboration equation [15]. Disease activity was scored at baseline (presentation with RAI) and follow-up using the Indian Takayasu Activity Index 2010 (ITAS2010) on a scale of 0–51 [16]. Organ damage was assessed at the last follow-up on a scale of 0–8 using the Vasculitis Damage Index [17].

Hypertension was defined as a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg or a normal blood pressure on antihypertensive medications. Worsening renal function was defined as a decrease in the eGFR $>20\%$ over the follow-up period and improvement in renal function was defined as an increase in eGFR $>20\%$. Stable renal function was defined as a change in the eGFR of $<20\%$. Renal size asymmetry was determined subjectively as reported by the reading radiologist on ultrasound, Tc99m mercaptoacetyltriglycine scan or angiography. Resolution of size asymmetry required the renal size to be normal bilaterally. Angiography was classified as stable if reported by the radiologist on follow-up imaging.

Statistical analyses

Data from all three sites were pooled. Descriptive analyses were used to describe the cohort. Data are presented as median and interquartile (IQR) range, mean and range or number and percentage unless stated otherwise.

Ethics

In accordance with UK National Health Service Research Ethics Committee guidelines, ethical approval was not required for this work because it comprises retrospective data and all treatment decisions were made prior to our evaluation. Patients seen in Canada provided informed and written consent to participate in the clinic database for the purpose of data collection. Study approval was obtained through the Mount Sinai Hospital Research Ethics Board (Research Ethics Application 14-0052-D Vasculitis Database). The study was also approved by the Regional Ethics Review Board, Lund, Sweden (2010/517).

Results

Cohort

A total of 122 cases with TAK were reviewed for RAI. Ten of 37 (27%) had RAI in the UK cohort, 6/13 (46%) in the Swedish cohort and 21/72 (29%) in the Canadian cohort. Overall, there were 37/122 TAK patients with RAI

Table 1 Renal and non-renal parameters according to baseline RAI

	Unilateral RAI ($n = 18$)		Bilateral RAI ($n = 19$)	
	Baseline	Follow-up	Baseline	Follow-up
RAI, *n* (%)				
Unilateral	18 (100)	9 (50)	0 (0)	3 (16)
Bilateral	0 (0)	1 (6)	19 (100)	10 (53)
Normal	N/A	7 (39)	N/A	3 (16)
No data	N/A	1 (6)	N/A	3 (16)
Renal parameters, *n* (%)				
HT	11 (61)	10 (56)	16 (84)	15 (79)
eGFR, median (IQR)	94 (86–107)	101.5 (85–107)	98 (73–135)	104 (89–124)
GFR <60 ml/min/1.73 m^2, *n* (%)	1 (6)	1 (6)	2 (11)	2 (11)
Renal asymmetry, *n* (%)	5 (28)	5 (28)	5 (26)	5 (26)
Non-renal parameters, median (IQR)				
ITAS2010	13 (9–15)	3 (0–6)	12 (9–14)	1 (0.5–5.5)
ESR	43 (32–55)	16 (10–24)	59 (36–101)	13 (8–27)
CRP	29 (9–45)	4.5 (2–20)	28 (13–65)	3.2 (1–6)
VDI	N/A	4.5 (3–5)	N/A	4 (3–7)

HT: hypertension; VDI: Vasculitis Damage Index.

(30%). Among these 37 patients, 18 patients (49%) had unilateral and 19 (51%) had bilateral involvement (Table 1). The severity of RAI was variable, ranging from mild/thickening/ectasia to severe/tight/high grade. Baseline patient demographics are summarized in Table 2. Thirty-three patients (89%) were female. The median age at diagnosis was 27 years (IQR 16–38). Seven were >40 years of age, including four >60 years of age; these patients did not have symptoms suggestive of nor did they meet ACR classification criteria for GCA [18]. Among the UK and Canadian cohorts, the median disease duration at first radiologic assessment was 0.5 years (IQR 0.2–2) but ranged from 0 to 26 years.

Twenty-nine patients (78%) met the ACR classification criteria for TAK. Six of eight patients that did not meet the criteria were young (between 9 and 18 years), one was 33 years and another was 64 years. All were diagnosed on the basis of positive angiography and elevated inflammatory markers, the latter not being an ACR criterion. At baseline, 22 patients (59%) had asymmetric blood pressures between arms, 19 (51%) had reduced brachial pulses, 16 (43%) reported symptoms of limb claudication and 13 (35%) had audible subclavian or abdominal bruits.

At diagnosis of RAI, 34 patients (91%) had elevated inflammatory markers. The median baseline CRP was 29 mg/l (IQR 9–57) and the median ESR was 44 mm/h (IQR 34–84). ITAS2010 scores were available at presentation in 35/37 patients; the median ITAS2010 was 13 (IQR 9–15).

Twenty-nine of 37 patients (78%) had comorbidities at diagnosis of RAI, which are summarized in Table 2. Pre-existing hypertension was present in 19 patients (51%). Two (5%) had pre-existing structural renal disease, including pelvi-ureteric junction obstruction with hydronephrosis and undefined renal surgery with hydronephrosis. SpA was present in six patients (16%), IBD in 3 (8%), psoriasis in 2 (5%) and seronegative arthropathy in 1 (3%). Three patients (8%) had previously been treated for tuberculosis.

Fourteen patients (38%) were treatment naïve at the diagnosis of RAI. Twenty-one patients (57%) had received prior systemic treatments (Table 2), including glucocorticoids (GCs) and immunosuppressive drugs (ISDs). Eight (22%) received GCs alone, 10 (27%) received GCs and one or more ISD and 3 (8%) received infliximab with or without GC/ISD. The most common ISDs were AZA (six patients), CYC (two patients) and MTX (two patients). MMF and ciclosporin were used in one patient each.

Follow-up

The median follow-up was 7 years (IQR 2–12) but ranged from 0 to 30 years. During that period of time, patients received both systemic and vascular treatments specific to RAI (Table 3).

In terms of systemic treatments, GCs alone were used in 4 patients (11%) and GCs in combination with an ISD in 29 (78%); 4 patients (11%) did not receive systemic therapy.

Conventional ISDs alone were used in 19 (51%) patients, most commonly AZA and MTX. Biologics were used in 10 (27%) patients: infliximab in 7 (19%), adalimumab in 2 (5%), and rituximab in 2 (5%). Abatacept was used in two patients (5%). Some patients received more than one biologic drug during the follow-up period, but not concurrently. At the last follow-up, 22 patients (59%) remained on GCs, among which at least 12 (32%) were on >5 mg/day of prednisone equivalent. Eight patients (21%) were on GCs alone. Twenty patients (54%) were on an ISD, most commonly AZA or MTX,

Table 2 Presenting baseline demographics of TAK patients with RAI

Patient demographics	Value
Patients, *n*	
Total	37
Cambridge, UK	10
Lund, Sweden	6
Toronto, Canada	21
Unilateral RAI, *n* (%)	18 (49)
Bilateral RAI, *n* (%)	19 (51)
Female, *n* (%)	33 (89)
Age, median (IQR), years	27 (16–38)
Ethnicity, *n* (%)	
White	20 (54)
Asian	7 (19)
Black	3 (8)
Other[a]	7 (19)
Disease duration, median (IQR), years	0.5 (0.2–2)
ACR classification met, *n* (%)	29 (78)
Disease features, *n* (%)	
Asymmetrical blood pressure	22 (59)
Reduced brachial pulse	19 (51)
Limb claudication	16 (43)
Bruit	13 (35)
Disease activity, ITAS2010, median (IQR)	13 (9–15)
Comorbidities, *n* (%)	
Hypertension	19 (51)
SpA[b]	6 (16)
Treated tuberculosis	3 (8)
Structural renal disease	2 (5)
Prior treatments, *n* (%)	
None	14 (38)
Systemic treatments	21 (57)
GC only	8 (22)
GC + more than one ISD	10 (27)
IFX ± GC + ISD	3 (8)
Endovascular intervention	2 (5)
CABG	1 (3)

[a]Other: Arabic (2), Hispanic (2), South Asian (2), undefined (1).
[b]SpA: IBD, psoriasis, seronegative inflammatory arthritis.
CABG: coronary artery bypass graft; IFX: infliximab.

Table 3 Pharmacologic and vascular treatments administered during the follow-up period

Treatments	Unilateral RAI (*n* = 18)	Bilateral RAI (*n* = 19)
Systemic treatments, *n* (%)		
GC alone	0 (0)	4 (21)
ISD ± GC	15 (83)	14 (73)
None	3 (16)	1 (5)
Number of antihypertensives, median (IQR)	1 (0–1.75)	1 (0.5–3)
Vascular treatments, *n* (%)		
Endovascular	2 (11)	3 (16)
Surgical	1 (6)	2 (11)

including two who were receiving rituximab and two who were receiving infliximab in addition to a conventional ISD. Nine were not receiving systemic therapy.

The median number of antihypertensive agents was 1 (IQR 0–2, range 0–6).

For vascular treatments, seven patients underwent eight vascular and/or surgical interventions for RAI, including five patients (14%) who had endovascular intervention (renal angioplasty and/or stent placement) and three patients (8%) who had surgical intervention. Among the five former patients, two had angioplasty alone (successful in one) and three had angioplasty with endovascular stent placement, including one who required successful rescue angioplasty after endovascular stent collapse. Among the three who underwent surgical intervention, one who had no systemic therapy underwent successful bilateral renal artery bypass, one underwent unilateral renal artery bypass (failed) with subsequent nephrectomy and one underwent splenorenal shunt (failed) subsequent to bilateral renal artery endovascular stent placement complicated by endovascular thrombosis, ultimately resulting in nephrectomy.

Outcomes

Table 1 summarizes renal and non-renal parameters at baseline (diagnosis of RAI) and follow-up stratified according to baseline RAI (unilateral *vs* bilateral). Follow-up angiography was available for 33 patients (89%). Ten patients (27%) had resolution of RAI.

Among the 18 patients (49%) with unilateral involvement at baseline, 9 (50%) had persistent unilateral RAI, 1 (6%) had progressed to develop bilateral RAI, 7 (39%) had resolution of RAI at follow-up and 1 (6%) had no follow-up angiography. Two patients with persistent unilateral RAI had reduced radiographic severity. Of those with resolution of RAI, one had a 'high-grade' stenosis and received systemic therapy and angioplasty, five received systemic therapy alone and one received no treatment.

Among the 19 patients (51%) with bilateral disease at baseline, 10 (53%) had persistent bilateral RAI at follow-up, 3 (16%) had improvement with unilateral RAI and 3 (16%) had complete resolution; follow-up data were not available for 3 (16%) patients. Two patients with persistent bilateral RAI had improvement in the severity of RAI and in six patients the severity remained the same; there were inadequate baseline data to comment on the change in severity for two patients. There was no follow-up angiography for three patients. All three patients with unilateral RAI at follow-up received systemic therapy, including an aforementioned patient who underwent splenorenal shunt complicated by nephrectomy. All three patients with complete resolution of RAI at follow-up received systemic therapy and one underwent angioplasty.

Twenty-seven patients (73%) were hypertensive or on antihypertensive therapies at the diagnosis of RAI, including 11 (61%) with unilateral and 16 (84%) with bilateral RAI (Table 1). In 10 patients, hypertension

predated the diagnosis of TAK, including one with pre-existing gestational hypertension. At follow-up, 25 (68%) patients had hypertension, including 10 (56%) with unilateral and 15 (79%) with bilateral RAI; 24/25 (96%) were on antihypertensive agents. Of these, 23 (92%) had hypertension at baseline. Four of 27 patients (15%) with hypertension at baseline were no longer hypertensive or on antihypertensive therapy at follow-up (2 with bilateral RAI at baseline). Among those with hypertension at follow-up, the median number of antihypertensive agents was 1 (IQR 1–3, range 0–6).

The median eGFR at diagnosis with RAI was 94 ml/min/1.73 m^2 (IQR 86–107) and 98 (73–135) for patients with unilateral and bilateral RAI, respectively. At follow-up this was largely unchanged (Table 1). Over the follow-up period, 7 showed an improvement in eGFR, 4 showed a decline and 21 had no change; follow-up eGFR was not available for 5 patients. At presentation with RAI, three patients (8%) were noted to have an eGFR $<$60 ml/min/1.73 m^2 but $>$45. One had severe unilateral disease and two had bilateral disease. All three patients had renal asymmetry. Among the three presenting with eGFR $<$60 ml/min/1.73 m^2, one patient showed an improvement in eGFR, one maintained eGFR and one had a worsening of eGFR in the context of known pre-existing pelvi-ureteric junction obstruction. At follow-up, two had an eGFR $<$60 ml/min/1.73 m^2, including one patient who previously had a normal eGFR.

Renal size asymmetry was present in 10 patients (27%) at diagnosis of RAI, including 5 (28%) with unilateral and 5 (26%) with bilateral disease, and was absent in 21 patients (57%). Data on renal asymmetry at the diagnosis of RAI were not available for six patients (16%); however, two of these patients had no asymmetry on angiography on the next available imaging. Two patients with renal asymmetry at the diagnosis of RAI had pre-existing structural defects, including pelvi-ureteric junction obstruction and hydronephrosis and undefined prior renal surgery. One patient was referred after failed stent placement. At follow-up, 10 patients (27%) had renal asymmetry, including 3 who developed new renal asymmetry, 2 of whom underwent nephrectomy. The remaining seven patients had pre-existing renal asymmetry. Three with renal size asymmetry at baseline had normalization of renal symmetry at follow-up. Renal symmetry data at follow-up were unavailable for two patients. Two other patients had no follow-up data available, but an angiogram done earlier showed no renal asymmetry.

Disease activity and organ damage

Follow-up ITAS2010 scores were available in 31/37 patients and the median was 2 (IQR 0–6). Overall, 28 patients experienced a reduction in the ITAS2010 score, indicating a reduction in disease activity. Two patients had stable ITAS2010 scores. In six, follow-up ITAS2010 scores were not available and in one a baseline ITAS2010 score was not available, making comparison impossible. The median Vasculitis Damage Index score at follow-up was 4 (IQR 3–5). The most common damage items recorded were major vessel stenosis ($n = 34$), diastolic hypertension ($n = 22$), claudication $>$3 months ($n = 16$), absent pulse ($n = 12$) and valvular heart disease ($n = 11$).

Pregnancies

Eight patients in the Canadian and Swedish cohorts had 12 pregnancies resulting in 8 healthy infants during the follow-up period. There were three therapeutic abortions. There were no maternal or foetal deaths.

Four patients with unilateral disease, including three with severe RAI, had six pregnancies resulting in four live healthy infants. Among the three with severe unilateral RAI, one was delivered by caesarean section at 36 weeks due to hypertension and severe oligohydramnios, one was delivered at term and one was therapeutically aborted at 9 weeks. One patient with unilateral RAI (undefined severity) had two healthy pregnancies and one therapeutic abortion.

Four patients with bilateral disease, including one with severe bilateral RAI, had six pregnancies resulting in four healthy infants. The patient with severe bilateral RAI delivered at 36 weeks gestation by caesarean section for severe gestational hypertension, one patient with mild bilateral RAI had two healthy pregnancies, one by normal vaginal delivery and one by caesarean section, and there was one therapeutic abortion. One patient with bilateral undefined RAI delivered at term by caesarean section. One patient with mild bilateral RAI was still pregnant during the study period.

Discussion

To our knowledge, this is the first publication describing the long-term outcomes of TAK with RAI in an ethnically diverse western cohort. The 30% prevalence of RAI involvement in the three cohorts studied here is comparable to that previously reported (8–46%) [3, 4, 6–8, 11, 19, 20], although it is higher than in Japanese cohorts [9, 10].

Hong *et al*. [11] recently described long-term outcomes of RAI in a Korean cohort of TAK patients. However, there are important differences in the study population and design as compared with our study. Our cohort is younger, more Caucasian and more ethnically diverse. Our cohort had similar rates of RAI and baseline and follow-up eGFRs, however, hypertension, refractory hypertension and death were less frequent. This may be attributed to milder disease, although it is difficult to compare. Hong *et al*. [11] did not include disease activity scores. Finally, while our study is a basic descriptive analysis, the Hong *et al.* study compares outcomes by vascular interventions.

ACR classification criteria were met in 78% of our patients. These criteria have limited utility in clinical practice, as four of the six criteria present late-disease findings rather than systemic signs, which present earlier

in the disease course. All our patients had abnormal angiograms suggestive of TAK, the majority had elevated inflammatory markers and all presented with systemic and vascular symptoms and signs highly suggestive for TAK. None presented with features of or met the criteria for GCA; these patients presumably had undiagnosed arterial lesions years before clinical diagnosis. The predominance of females and the mean age of our cohort are comparable to previous reports [3, 4, 6, 8, 10, 19, 20].

Hypertension was the most commonly reported pre-existing comorbidity in our study, occurring in 51% of patients, which is significantly more frequent than many published cohorts but similar to the previously published cohort of patients with TAK and RAI [11]. This may be due to underlying RAI; a study comparing TAK patients with and without RAI would elucidate this. The majority of patients were on antihypertensive agents at follow-up. Interestingly, we noticed an increased association of SpA features, including IBD, which has been previously described [21, 22], as well as seronegative inflammatory arthritis and psoriasis. The incidence of previously treated tuberculosis was elevated and has been previously linked to TAK [23].

The median follow-up period of patients was 7 years. The four with a decline in renal function had a longer follow-up period (range 7–24 years), which may account for this decline. During the follow-up period the majority of patients were on systemic therapies. A minority underwent vascular interventions for severe RAI, including both endovascular and surgical repair, and half of these were complicated. Despite poor angiographic outcomes, these patients did not experience end-stage renal disease (ESRD).

RAI in TAK is commonly described as a poor prognostic marker due to its association with renovascular hypertension and subsequent complications, but there are few data to support this [4, 6, 7, 12]. The results of this study are reassuring, as in the majority of patients, angiography results improved over time. Renal asymmetry was uncommon at baseline and, when present, was associated with structural renal disease; patients did not develop renal asymmetry over time. Hypertension was common at baseline and follow-up; however, the majority of patients were not on more than three antihypertensive agents. The majority of patients had normal eGFRs at baseline and follow-up. In general, eGFRs were stable over time, with eGFRs declining in only four patients. The lowest eGFR was still $>$40 ml/min/1.73 m^2, representing stage 3B chronic kidney disease; none of our patients experienced ESRD and there were no deaths. Overall, the study demonstrates that the long-term renal and survival outcomes of TAK patients with RAI are more favourable than previously thought in an ethnically diverse western cohort.

Pregnancy outcomes in this TAK cohort were favourable and comparable to other published cohorts [24–26]. While gestational hypertension resulted in preterm caesarean section, there were no reports of pre-eclampsia and no maternal or foetal deaths. Data on miscarriages were not recorded.

The strengths of this study include the relatively large size of the cohort of ethnically diverse patients with a rare disease from multiple sites and the length of follow-up and retention over time. However, the study is limited by the nature of its design as a retrospective chart review, leading to some missing data and potential inaccuracies in activity and damage assessment. It is also not possible to assess the contribution of expert multidisciplinary management in disease outcomes.

In conclusion, our study demonstrated a favourable long-term outcome of RAI in a large, multicentre, ethnically diverse cohort of patients with TAK. Renal outcomes were favourable regardless of unilateral or bilateral disease and disease severity. However, the impact of the clinical care of these patients at expert vasculitis centres, with long-term systemic and antihypertensive therapy, may have impacted the outcomes.

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